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invention, and should not be construed as the surrender this subject matter. Claims 2, 4, 5, 13, 19 and 46 are amended.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 2-12 are rejected by the Examiner as allegedly being indefinite. The Examiner alleges that claim 2 is indefinite in the definition of the "corresponding wild-type AAV Rep 78." The Examiner states that no reference sequence for the wild-type Rep 78 is apparent. Applicant points out that the specification discloses that the wild-type AAV Rep 78 protein is a non-mutated AAV Rep 78 protein from which the modified AAV Rep 78 proteins are derived. As stated on page 19, lines 15-21, the wild-type AAV Rep 78 protein is disclosed in SEQ ID NO:6 and also in Figure 16. Although applicant believes that it is clear from the claims read in light of the specification that the wild-type AAV Rep 78 protein is sufficiently defined, in an effort to expedite prosecution, claim 2 has been amended to reference the known sequence of this protein.

The Examiner maintains that the "bind differently" phrase of claim 2 is indefinite. Applicant again points to page 12, lines 11-13 and 23-26 which states that the AAV Rep78 mutants either possess enhanced or weakened DNA binding to other viral DNA as compared to the wild-type AAV Rep78 protein's binding to the same viral DNA. However, in an effort to expedite prosecution, applicant has included the language of claim 3 into claim 2.

The examiner maintains that claim 7 is indefinite in the recitation of "minimum number of amino acids" of the wild-type AAV Rep78 protein that are necessary to bind to the desired DNA sequences. Applicant points out that the wild-type AAV Rep78 protein has been identified by a specific sequence in claim 2 which provides a defined sequence. As noted in the last response, the specification provides assays to determine binding of the AAV Rep 78 proteins to DNA sequences. Thus, a person of skill in the art would be able to determine through trial and error experimentation the minimum number and location of amino acids that are necessary to bind to the DNA sequence to obtain enhanced inhibition of papillomavirus or an oncogene without undue experimentation.

The Examiner rejects claims 13-20 and 47 as indefinite for the recitation of "bind ...differently." Again in an effort to expedite prosecution, applicant has included the language of claim 47 in amended claim 13. Claim 13 has also been amended to delete

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reference to "a wild-type AAV Rep 78 protein" as requested by the Examiner because he considers the recitation of this phrase is to non-elected subject matter.

As with claim 13, the Examiner additionally alleges that claim 19 references non-elected subject matter in its recitation of "a wild-type AAV Rep 78 protein." Applicant has amended claim 19 to delete this language and also has deleted the term "admixture" as requested by the Examiner. Applicant considers the pharmaceutical composition to be a mixture of the protein and the pharmaceutical carrier.

In view of the above comments and amendments to clarify the invention and not to limit it, it is requested that these rejections be withdrawn with regard to rejected claims.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 2-20 and 46-47 are rejected by the Examiner as allegedly only being enabled for the specifically exemplified AAV Rep modified proteins because the specification does not enable other mutants and/or modified proteins of the AAV Rep 78 protein. The Examiner admits that the specification does provide guidance as to how to AAV Rep 77^{LG}, 79^{FA}, and 192^{HG} modified proteins were prepared and cites *In re Wands* in support of his position.

Applicant respectfully disagrees with the Examiner's position because carrying out standard experimentation to modify a known amino acid sequence and then assaying for the binding activity of the modified proteins to known binding partners does not require undue experimentation. It only requires following the methods provided in the specification to prepare the exemplified AAV Rep 78 mutants by performing standard experimental methods known to persons skilled in the art. Additionally, the examples provided in the present specification to prepare AAV Rep 77^{LG}, 79^{FA}, and 192^{HG} modified proteins can be used to prepare other mutants proteins. As noted previously, the amino acid and nucleic acid sequences are known and provided in the specification, figures and Sequence Listing. Plasmids containing a specific Rep 78 mutant can be prepared using different mutagenic oligonucleotides. All of the manipulations to create other mutant proteins from known sequences are well within the skill of the artisan. The specification beginning on page 19 discloses the construction of AAV Rep 78 mutant plasmids and proteins. Additionally the specification provides assays to determine the binding of the AAV Rep78 mutant proteins to DNA sequences. Thus, a person of skill in the art would be able to determine through trial

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and error experimentation other AAV Rep 78 proteins using the guidance in the specification for making AAV Rep 77^{LG}, 79^{FA}, and 192^{HG} modified proteins.

The court in *In re Wands*, 8 USPQ 1400, 1403-1407 (Fed. Cir. 1988) found the invention enabled and reversed the decision of the Board of Appeals and Patent Interferences. The court held that the specification was enabling because "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed", and "all of the methods needed to practice the invention were known." The court further laid out a number of factors to be considered when assessing the enablement requirement and whether any experimentation was undue. The court stated that it is improper to make an enablement determination based on the analysis of only one of these factors without consideration of the other factors. Any conclusion must be based on the evidence as a whole after considering any evidence related to each of these factors. *Id* at 1404 and 1407.

The Examiner has cited Batchu as disclosing a AAV Rep 78 mutant that lacks the ability to bind DNA and lacks the ability to replicate as supporting unpredictability in the art but the properties of the mutants can be tested for using the guidance and assays in the specification. Only trial and error experimentation is required to determine the properties of the mutants made by the method of the present invention.

The Examiner also states that the specification provides guidance for making AAV Rep 77^{LG} that can be used to make AAV Rep 79^{FA} and 192^{HG} modified proteins. But if AAV Rep 77^{LG} can be used to make the other two modified proteins then it also can be utilized to make other AAV Rep 78 mutants. The amino acid and nucleic acid sequences of AAV Rep 78, methods of making the AAV Rep mutants and methods for assaying for their binding is disclosed in the present application and it would not require undue experimentation to make other AAV Rep 78 modified proteins.

The Examiner states that the specification is not enabled for the myriad of possible AAV Rep 78 mutants but applicant disagrees. The testing to determine the mutants that have binding that is weaker or enhanced as compared to the wild-type Rep 78 protein is routine. "The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides

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a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id* at 1404.

Applicant requests the this rejection be withdrawn in view of these arguments.

CONCLUSION

The present response is intended to be a complete response to the Examiner's Office Action. It is believed that the above arguments and amendments to the claims place the application in condition for allowance, and a notice to that effect is respectfully requested. If there are any minor issues which can be taken care by telephone, it is requested that the Examiner contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

Date

December 10, 2002

By

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Marked-Up Copy of Claims:

2. (Amended) An adeno-associated virus (AAV) Rep78 mutant comprising an AAV Rep78 modified protein that binds to at least one DNA sequence obtained from one or more of a papillomavirus, an AAV, an oncogene or a HIV differently as compared to the binding of the corresponding wild-type AAV Rep78 protein **as set forth in SEQ ID NO:6, wherein said different DNA binding is selected from the group consisting of no DNA binding, weak DNA binding and enhanced DNA binding as compared to the binding of said wild-type AAV Rep78 protein.**

4. (Amended) The AAV Rep78 mutant of claim [3] 2, wherein said AAV Rep78 modified protein having no DNA binding or weak DNA binding to said DNA sequence obtained from at least one of a papillomavirus, an AAV, an oncogene or a HIV that results in the generation of higher levels of AAV DNA replication and virion numbers.

5. (Amended) The AAV Rep78 mutant of claim [3] 2, wherein said AAV Rep78 modified protein having enhanced DNA binding to said DNA sequence obtained from at least one of a papillomavirus or an oncogene that results in enhanced inhibition of at least one of a papillomavirus or an oncoprotein.

13. (Amended) A fusion protein comprising [a wild-type AAV Rep78 protein or] an AAV Rep78 modified protein that binds to at least one DNA sequence obtained from one or more of a papillomavirus, an AAV, an oncogene or a HIV differently as compared to the binding of [said] **the corresponding** wild-type AAV Rep78 protein **as set forth in SEQ ID NO:6**, and that results in AAV DNA replication and/or AAV virion production, **wherein said different DNA binding is selected from the group consisting of no DNA binding, weak DNA binding and enhanced DNA binding as compared to the binding of said wild-type AAV Rep78 protein.**

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19. (Amended) A pharmaceutical composition comprising at least one AAV Rep78 mutant according to claim 2 [or an AAV Rep 78 protein, in admixture] with a pharmaceutically acceptable carrier.

46. (Amended) The AAV Rep78 mutant of claim 2, wherein said binding results in AAV DNA replication and/or AAV virion production.